#### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner

Not yet assigned

Group Art Unit

Not yet assigned

Applicants

Frederick B. Oleson et al.

Serial No.

Not yet assigned

Filed

Concurrently herewith

For

METHODS FOR ADMINISTRATION OF ANTIBIOTICS

New York, New York February 20, 2002

Hon. Commissioner for Patents Washington, D.C. 20231

# TRANSMITTAL LETTER FOR INFORMATION DISCLOSURE STATEMENT

Sir:

Transmitted herewith is an Information Disclosure Statement in the aboveidentified application. This Statement is submitted:

[X] within three months of the application filing date;

[] more than three months from the application filing date but before the mailing date of the first Office Action on the merits.

In accordance with 37 C.F.R. § 1.97, submission of this Statement requires no fee. However, if for any reason a fee is due, the Director is hereby authorized to charge payment of any fees required in connection with this Information Disclosure

Statement to Deposit Account No. 06-1075. A duplicate copy of this letter is transmitted herewith.

Respectfully submitted,

Harry E. Brown James F. Haley, Jr. (Reg. No. 27,794)

Attorney for Applicants

Karen E. Brown (Reg. No. 43,866)

Agent for Applicants

c/o FISH & NEAVE 1251 Avenue of the Americas New York, NY 10020-1104

Tel: (212) 596-9000

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner

Not yet assigned

Group Art Unit

Not yet assigned

Applicants

Frederick B. Oleson et al.

Serial No.

Not yet assigned

Filed

Concurrently herewith

For

METHODS FOR ADMINISTRATION OF

ANTIBIOTICS

New York, New York February 20, 2002

Hon. Commissioner for Patents Washington, D.C. 20231

## INFORMATION DISCLOSURE STATEMENT

Sir:

Pursuant to 37 C.F.R. §§ 1.56 and 1.97, applicants make of record the

following documents which are listed on the enclosed Form PTO-1449.\*

<sup>\*</sup> Pursuant to 37 C.F.R. 1.98(d), applicants have not provided copies of the United States patents, foreign patent documents and other documents cited herein. These patents and documents were previously submitted to or cited by the Office in United States Patent Application 09/406,568, from which this application claims priority under 35 U.S.C. § 120. The information disclosure statements submitted in United States Patent Application 09/406,568 complied with 37 C.F.R. 1.98 (a) through (c).

#### UNITED STATES PATENTS

Re. 32,310	Debono	issued December 16, 1986
Re. 32,311	Debono	issued December 16, 1986
Re. 32,333	Hamill	issued January 20, 1987
Re. 32,455	Hamill	issued July 7, 1987
4,482,487	Abbott	issued November 13, 1984
4,524,135	Abbott	issued June 18, 1985
4,537,717	Abbott	issued August 27, 1985
4,800,157	Eaton	issued January 24, 1989
4,874,843	Baker	issued October 17, 1989
4,885,243	Huber	issued December 5, 1989
5,912,226	Baker	issued June 15, 1999*

### FOREIGN PATENT DOCUMENTS

EP 0 386 951	published September 12, 1990
WO 98/22107	published May 28, 1998
WO 99/30728	published June 24, 1999

#### OTHER DOCUMENTS

Woodworth et al., "Single-Dose Pharmacokinetics and Antibacterial Activity of Daptomycin, a New Lipopeptide Antibiotic, in Healthy Volunteers," Antimocrobial Agents and Chemotherapy 36: 318-325, 1992.

Currently in reissue as application 09/547,357, filed April 11, 2000.

Woodworth et al., "Tobramycin and Daptomycin Disposition When Co-Administered to Healthy Volunteers," *Journal of Antimicrobial Chemotherapy* 33:655-659, 1994.

Bernard et al., "Pharmacokinetics and Suction Blister Fluid Penetration of a Semisynthetic Injectable Streptogramin RP59500 (RP 57699/RP54476)," Eur. J. Clin. Microbiol. Infect. Dis. 13: 768-771, 1994.

Tally et al., "Daptomycin: A Novel Agent for Gram-Positive Infections," Exp. Opin. Invest. Drugs 8:1223-1238, 1999.

Moellering et al., "The Efficacy and Safety of Quinupristin/Dalfopristin for the Treatment of Infections Caused by Vancomycin-Resistant Enterococcus faecium," Journal of Antimicrobial Chemotherapy 44: 251-261, 1999.

Richard H. Baltz, "Lipopeptide Antibiotics Produced by Streptomyces roseosporus and Streptomyces fradiae," *Biotechnology of Antibiotics* 2d Ed., 415-435, 1997.

Boxenbaum et al., "Interspecies Pharmacokinetic Scaling, Biological Design and Neoteny," Advances in Drug Research 19: 139-196, 1990.

Caron et al., "Daptomycin or Teicoplanin in Combination with Gentamicin for Treatment of Experimental Endocarditis Due to a Highly Glycopeptide-Resistant Isolate of Enterococcus faecium," *Antimicrobial Agents and Chemotherapy* 36:2611-2616, 1992.

Flandrois et al., "Early Stages of In Vitro Killing Curve of LY146032 and Vancomycin for Staphylococcus aureus," *Antimicrobial Agents and Chemotherapy* 32:454-457, 1988.

Freireich et al., "Quantitative Comparison of Toxicity of Anticancer Agents in Mouse, Rat, Hamster, Dog, Monkey, and Man," Cancer Chemotherapy Reports 50: 219-244, 1966.

Garrison et al., "Suboptimal Effect of Daptomycin in the Treatment of Bacteremias," Southern Medical Journal 82: 1414-1415, 1989.

Garrison et al., "Assessment of Effects of Protein Binding or Daptomycin and Vancomycin Killing of Staphylococcus aureus by Using an In Vitro Pharmacodynamic Model," *Antimicrobial Agents and Chemotherapy* 34: 1925-1931, 1990.

Gray et al., "Antibiotic-resistant enterococci," Journal of Hospital Infection 21:1-14, 1992.

Hanberger et al., "Pharmacodynamics of Daptomycin and Vancomycin on Enterococcus faecalis and Staphylococcus aureus Demonstrated by Studies of Initial Killing and Postantibiotic Effect and Infuence of Ca<sup>2+</sup> and Albumin on These Drugs," Antimicrobial Agents and Chemotherapy 35: 1710-1716, 1991.

Kaatz et al., "Daptomycin Compared with Teicoplanin and Vancomycin for Therapy of Experimental Staphylococcus aureus Endocarditis," Antimicrobial Agents and Chemotherapy 34: 2081-2085, 1990.

Lamp et al., "In Vitro Pharmacodynamic Effects of Concentration, pH, and Growth Phase on Serum Bactericidal Activities of Daptomycin and Vancomycin," Antimicrobial Agents and Chemotherapy 36: 2709-2714, 1992.

Lee et al., "Daptomycin versus Conventional Therapy in the Treatment of Endocarditis and Bacteremia," Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, A885, 1991.

Lee et al., "Effect of Protein Binding of Daptomycin on MIC and Antibacterial Activity," *Antimicrobial Agents and Chemotherapy* 35: 2505-2508, 1991.

Low et al., "Enterococcis: Pathogens of the 90s," *The European Journal of Surgery Suppl.* 573: 19-24, 1994.

Ole-Mapenay et al., "Aspects of the Pharmacokinetics of Doxycycline Given to Healthy and Pneumonic East African Dwarf Goats by Intramuscular Injection," *Veterinary Research Communications* 21: 453-462, 1997.

Prieur et al., "Clinical Toxicologic Evaluation of Cancer Chemotherapeutic Agents: Protocols of the Laboratory of Toxicology," *Cancer Chemotherapy Reports* 4: 1-30, 1973.

Ramos et al., "Comparison of Daptomycin, Vancomycin, and Ampicillin-Gentamicin for Treatment of Experimental Endocarditis Caused by Penicillin-Resistant Enterococci," *Antimicrobial Agents and Chemotherapy* 36: 1864-1869, 1992.

Rotschafer et al., "Therapeutic Update on Glycopeptide and Lipopeptide Antibiotics," *Pharmacotherapy* 8:211-219, 1988.

Rybak et al., "Pharmacokinetics and Bactericidal Rates of Daptomycin and Vancomycin in Intravenous Drug Abusers Being Treated for Gram-Positive

Endocarditis and Bacteremia," Antimicrobial Agents and Chemotherapy 36: 1109-1114, 1992.

Sexton et al., "The Use of Daptomycin, a Lipopeptide Antibiotic, in the Treatment of Gram Positive Infections in Man," Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, A932, 1988.

Stratton et al., "Bactericidal Activity of Deptomycin (LY146032) Compared with Those of Ciprofloxacin, Vancomycin, and Ampicillin against Enterococci as Determined by Kill-Kinetic Studies," *Antimicrobial Agents and Chemotherapy* 31: 1014-1016, 1987.

Stratton et al., "Effect of Human Serum on the Bactericidal Activity of Daptomycin and Vancomycin Against Staphylococcal and Enterococcal Isolates as Determined by Time-Kill Kinetic Studies," Diagnostic Microbiology and Infectious Disease 13: 245-252, 1990.

Tally et al., "Daptomycin: a novel agent for Gram-positive infections," Exp. Opin. Invest Drugs 8: 1223-1238, 1999.

Thompson, "Dosage Regimen Design: A Pharmacokinetic Approach," Journal of Clinical Pharmacology 32: 210-214, 1992.

Vemuri et al., "Enterococcal infections: The increasing threat of nosocomial spread and drug resistance.," *Journal of Postgraduate Medicine* 93: 121-128, 1993.

Voorn et al., "Role of Tolerance in Treatment and Prophylaxis of Experimental Staphylococcus areus Endocarditis with Vancomycin, Teicoplanin, and Daptomycin," Antimicrobial Agents and Chemotherapy 38: 487-493, 1994.

Bayer, Arnold S., et al., "LY146032 Compared with Penicillin G in Experimental Aortic Valve Endocarditis Caused by Group G Streptococci," Antimicrobial Agents and Chemotherapy 32: 141-143 (1988).

Beauchamp, Denis, et al., "Effects of Daptomycin and Vancomycin on Tobramycin Nephrotoxicity in Rats," *Antimicrobial Agents and Chemotherapy* 34: 139-147 (1990).

Black, H.R., et al., "Preliminary Pharmacology and Pharmacokinetics of LY146032, A New Peptolipide Antibiotic," *Program and Abstracts of the 1986 Interscience Conference on Antimicrobial Agents and Chemotherapy*, p. 261, Abstract 894 (1986).

Bush, Larry M., et al., "Daptomycin (LY146032) Treatment of Experimental Enterococcal Endocarditis," *Antimicrobial Agents and Chemotherapy* 32: 877-881 (1988).

Bryant, R.E., et al., "Effect of Abscess Milieu on Bactericidal Activity of LY146032 Against Staphylococci," Eur. J. Clin. Microbiol. 6: 186-188 (1987).

Cantoni, L., et al., "Comparative Efficacy of Daptomycin, Vancomycin, and Cloxacillin for the Treatment of Staphylococcus aureus Endocarditis in Rats and Role of Test Conditions in this Determination," Antimicrobial Agents and Chemotherapy 34: 2348-2353 (1990).

Dougherty, Steven H., et al., "Impact of LY146032 on Streptococcus (Enterococcus) faecalis Translocation in Mice," Antimicrobial Agents and Chemotherapy 32: 337-340 (1988).

Dong, Mei-Yan, et al., "Treatment of Clostridium difficile Colitis in Hamsters with a Lipopeptide Antibiotic LY 146032," *Antimicrobial Agents and Chemotherapy* 32: 1135-1136 (1987).

Eliopoulos, George M., et al., "In Vitro and In Vivo Activity of LY 146032, a New Cyclic Lipopeptide Antibiotic," *Antimicrobial Agents and Chemotherapy* 30: 532-535 (1986).

Gorbach, Sherwood L., et al., "Treatment of Infectious Diseases," Infectious Diseases 2d Ed., 176, 190 (1998).

Haworth, Charles S., et al., "Staphylococcus aureus Ventriculitis Treated with Single-Dose Intraventricular Vancomycin or Daptomycin (LY146032): Bacterial and Antibiotic Kinetics in Hydrocephalic Rabbits," *Antimicrobial Agents and Chemotherapy* 34: 245-251 (1990).

Hindes, R.G., et al., "Treatment of Experimental Endocarditis Caused by a B-Lactamase-Producing Strain of Enterococcus faecalis with High-Level Resistance to Gentamicin," Antimicrobial Agents and Chemotherapy 33: 1019-1022 (1989).

Kephart, Phyllis A., et al., "Comparison of the Investigational Drug, LY 146032 with Vancomycin in Experimental Pneumonia Due to Methicillin-Resistant Staphylococcus aureus," *Journal of Antimicrobial Chemotherapy* 21: 33-39 (1988).

Kuechle, David K., et al., "Elution of Vancomycin, Daptomycin, and Amikacin from Acrylic Bone Cement," Clinical Orthopedics and Related Research 264: 302-308 (1991).

- Leggett, J., et al., Pharmacodynamic and Pharmacokinetic Parameters (PKPs) Affecting Activity of LY 146032 Against Staphylococcus aureus" Program and Abstracts of the 1986 Interscience Conference on Antimicrobial Agents and Chemotherapy, p. 123, Abstract 154 (1987).
- Li, T., et al., "In Vivo Efficacy of Daptomycin Against Systemic Infection Induced by Vancomycin-Resistant Enterococcus faecalis (VRE) in the Mouse," *Interscience Conference on Antimicrobial Agents and Chemotherapy*, Abstract F-116 (Sept. 24-27, 1998).
- Li, Tongchuan, et al., "Daptomycin Efficacy Against Vancomycin-Resistant Enterococcus faecalis (VRE) Induced Pyelonephritis in the Mouse,"

  Interscience Conference on Antimicrobial Agents and Chemotherapy Poster #1003 (Sept. 26-29, 1999).
- Li, Tongchuan, et al., "Effect of Oral Daptomycin on Vancomycin-Resistant Enterococcus Faecium (VREF) Gastrointestinal Tract Colonization in Antibiotic Treated Mouse," Infectious Disease Society of America Meeting, Abstract #244-Sa (Nov. 12-15, 1998).
- Louie, Arnold, et al., "The Pharmacodynamics of Daptomycin as Determined for Staphylococcus aureus in a Mouse Thigh Infection Model," Interscience Conference on Antimicrobial Agents and Chemotherapy Poster #1770 (Sept. 26-29, 1999).
- Luu, Q.N., et al., "Treatment of Chronic Experimental Staphylococcus aureus Osteomyelitis with LY146032 and Vancomycin," Eur. J. Clin. Microbiol. Infect. Dis. 8: 562-563 (1989).
- Mader, Jon T., et al., "Comparative Evaluation of Daptomycin (LY146032) and Vancomycin in the Treatment of Experimental Methicillin-Resistant Staphylococcus aureus Osteomyelitis in Rabbits," *Antimicrobial Agents and Chemotherapy* 33: 689-692 (1989).
- Michiels, Marie-Jose, et al., "Differential Increased Survival of Staphylococci and Limited Ultrastructural Changes in the Core of Infected Fibrin Clots after Daptomycin Administration," *Antimicrobial Agents and Chemotherapy* 40: 203-211 (1996).
- Miniter, Peggy M., et al., "Activity of LY146032 In Vitro and in Experimental Enterococcal Pyelonephritis," *Antimicrobial Agents and Chemotherapy* 31: 1199-1203 (1987).
- Nord, C.E., et al., "LY146032 Treatment of Clostridium difficile Colitis in Hamsters," Eur. J. Clin. Microbiol 6: 686 (1987).

- Rice, Louis B., et al., "In Vivo Activity of the Combination of Daptomycin and Fosfomycin Compared with Daptomycin Alone Against a Strain of Enterococcus faecalis with High-Level Gentamicin Resistance in the Rat Endocarditis Model," Diagn. Microbiol. Infect. Dis. 15: 173-176 (1992).
- Safdar, N., et al. "In-Vivo Pharmacodynamic Activity of Daptomycin (DAP) Against Multiple Bacterial Pathogens," Interscience Conference on Antimicrobial Agents and Chemotherapy Poster #1769 (Sept. 26-29, 1999).
- Sapico, Francisco L., et al., "LY146032, Alone and in Combination with Gentamicin, for the Treatment of Enterococcal Pyelonephritis in the Rat Model," Antimicrobial Agents and Chemotherapy 32: 81-83 (1988).
- Smith, K., et al., "Daptomycin Versus Vancomycin Treatment for Staphylococcus Aureus Bacteremia in a Murine Model," *Chemotherapy* 36: 428-434 (1990).
- Verghese, Abraham, et al., "LY146032 in a Hamster Model of Staphylococcus aureus Pneumonia: Effect on In Vivo Clearance and Mortality and In Vitro Opsonophagocytic Killing," *Chemotherapy* 34: 497-503 (1988).
- Wheat, Lawrence J., et al., "Comparison of Cefazolin, Cefamandole, Vancomycin, and LY146032 for Prophylaxis of Experimental Staphylococcus epidermidis Endocarditis," *Antimicrobial Agents and Chemotherapy* 32: 63-67 (1988).
- Wood, Craig A., et al., "Influence of Daptomycin on Staphylococcal Abscesses and Experimental Tobramycin Nephrotoxicity," *Antimicrobial Agents and Chemotherapy* 33: 1280-1285 (1989).
- Oleson, F.B., et al., "Once-Daily Dosing in Dogs Optimizes
  Daptomycin Safety," Antimicrobial Agents and Chemotherapy, 44: 2948-2953 (2000).
- LeClercq, R. et al., "Effects of Combinations of Beta-Lactams, Daptomycin, Gentamicin, and Glycopepties Against Glycopeptide-Resistant Enterococci," Antimicrobial Agents and Chemotherapy 35: 92-98 (1991).
- Watanakunakorn, J. "In Vitro Activity of LY 146032, a Novel Cyclic Lipopeptide, Alone or in Combination with Gentamicin or Tobramycin Against Enterococci," Antimicrobial Chemotherapy 19: 445-48 (1987).
- Thibault, N. et al., "Protection Against Gentamicin Nephrotoxicity by Daptomycin in Nephrectomized Rats," Life Sciences 22: 1877-87 (1995).

Etienne et al., "A Phase I, Double-Blind, Placebo-Controlled Study of the Tolerance and Pharmokinetic Behaviour of RP 59500," J. Antimicrobial Chemotherapy 30, Supp. A: 123-131 (1992), abstract only.

Griswold et al., "Quinupristin-Dalfopristin (RP 59500): An Injectable Streptogramin Combination," *American J. Health-System Pharmacy* 53: 2045-2053 (1996), abstract only.

Remington's Pharmaceutical Sciences, 17th Ed., pp. 1176-1213 (1985).

Van der Auwera, "Ex Vivo Study of Serum Bactericidal Titers and Killing Rates of Daptomycin (LY 146032) Combined or Not Combined with Amikacin Compared with Those of Vancomycin," *Antimicrobial Agents and Chemotherapy* 33: 1783-1790 (1989).

Kennedy et al., "Daptomycin (LY 146032) for Prevention and Treatment of Experimental Aortic Valve Endocarditis in Rabbits," *Antimicrobial Agents and Chemotherapy* 33: 1522-25 (1989).

Pryka et al., "Clinical Pharmacokinetics of Daptomycin," DICP The Annals of Pharmacotherapy 24: 255-56 (1990).

Akins, R.L., et al., "Activity of Daptomycin (D), Arbekacin (A), Vancomycin (V) and Gentamicin (G) Against Two Clinical Strains of Vancomycin-Intermediate Resistant Staphylococcus Aureus (VISA) in an In Vitro Pharmacodynamic Infection Model (IVPM)," Interscience Conference on Antimicrobial Agents and Chemotherapy Poster #1771 (1999).

Akins, R.L., et al., "Bactericidal Activities of Two Daptomycin Regimens Against Clinical Strains of Glycopeptide Intermediate-Resistant Staphylococcus Aureus, Vancomycin-Resistant Enterococcus Faecium, and Methicillin-Resistant Staphylococcus Aureus Isolates in an In Vitro Phamacodynamic Model with Simulated Endocardial Vegetations," Antimicrobial Agents and Chemotherapy 45(2): 454-459 (Feb. 2001).

Akins, R.L., et al., "In Vitro Activities of Daptomycin, Arbekacin, Vancomycin, and Gentamicin Alone and/or in Combination Against Glycopeptide Intermediate-Resistant Staphylococcus Aureus in an Infection Model," \*Antimicrobial Agents and Chemotherapy 44(7): 1925-1929 (July 2000).

Akins, R.L., et al., "Pharmacodynamics of Daptomycin (D) Against Vancomycin-Resistant Enterococcus faecium (VREF) and Methicillin-Resistant Staphylococcus aureus (MRSA) in an In Vitro Infection Model With Simulated Endocardial Vegetations (SEVs)," American Society of Microbiology Poster #A-19 (2000).

- Alborn, Jr., W.E., et al., "Daptomycin Disrupts Membrane Potential in Growing Staphylococcus Aureus," *Antimicrobial Agents and Chemotherapy* 35(11): 2282-2287, (Nov. 1991).
- Allen, N.E., "LY146032 Inhibits the Biosynthesis of Cell Wall Peptidoglycan in Gram-Positive Bacteria," Program and Abstracts of the Twenty-Fourth Interscience Conference on Antimicrobial Agents and Chemotherapy p. 281, Abstract 1081 (Oct. 8-10, 1984).
- Allen, N.E., et al., "Inhibition of Peptidoglycan Biosynthesis in Gram-Positive Bacteria by LY146032," *Antimicrobial Agents and Chemotherapy* 31(7): 1093-1099, (July 1987).
- Allen, N.E., et al., "Inhibition of Membrane Potential-Dependent Amino Acid Transport by Daptomycin," *Antimicrobial Agents and Chemotherapy* 35(12): 2639-2642, (Dec. 1991).
- Anaizi, N., "Once-Daily Dosing of Aminoglycosides A Consensus Document," *International Journal of Clinical Pharmacology and Therapeutics* 35 (6): 223-226 (1997).
- Andreasen, Jr., James R., et al., "Salinomycin Toxicosis in Male Breeder Turkeys," *Avian Diseases* 39: 638-642 (1995).
- Appleman, M.D., et al., "In Vitro Activities of Daptomycin (Cidecin<sup>TM</sup>), Linezolid, Quinupristin/Dalfopristin, Ziracin, and Vancomycin Against 255 Unique Clinical Isolates of Oxacillin-Resistant Staphylococcus Aureus Isolated Over Four Years (1996-1999)," Interscience Conference on Antimicrobial Agents and Chemotherapy Poster #2291 (2000).
- Aronoff, George R., et al., "Aminoglycoside Accumulation Kinetics in Rat Renal Parenchyma," *Antimicrobial Agents and Chemotherapy*, 23(1): 74-78 (Jan. 1983).
- Aronoff, G.R., et al., "LY146032 Kinetics in Normal Subjects and Patients With Renal Insufficienty," Program and Abstracts of the Twenty-Fourth Interscience Conference on Antimicrobial Agents and Chemotherapy, p. 132, Abstract 125 (Oct. 23-26, 1988).
- Barelay, Murray L., et al., "What is the Evidence for Once-Daily Aminoglycoside Therapy?," Clin. Pharmacokinet. 27(1): 32-48 (1994).
- Barry, Arthur L., et al., "In Vitro Activities of Daptomycin Against 2,789 Clinical Isolates from 11 North American Medical Centers," *Antimicrobial Agents and Chemotherapy* 45(6): 1919-1922 (June 2001).

Beauchamp, Denis, et al., "Subcellular Distribution of Daptomycin Given Alone or with Tobramycin in Renal Proximal Tubular Cells," *Antimicrobial Agents and Chemotherapy* 38(2): 189-194 (Feb. 1994).

Benson, Constance A., et al., "Comparative In-Vitro Activity of LY146032 a New Peptolide, with Vancomycin and Eight Other Agents against Gram-Positive Organisms," *Journal of Antimicrobial Chemotherapy* 20: 191-196 (1987).

Bergan, Tom, "Kinetics of Tissue Penetration," Scand J Infect Dis. Suppl. 14: 36-46 (1978).

Bergan, Tom, "Pharmacokinetics of Tissue Penetration of Antibiotics," Reviews of Infectious Diseases 3(1): 45-66 (Jan-Feb. 1981).

Bergeron, Michel G., "Tissue Penetration of Antibiotics," Clinical Biochemistry 19: 90-100 (April 1986).

Bingen, E., et al., "Bactericidal Activity of Vancomycin, Daptomycin, Ampicillin and Aminoglycosides against Vancomycin-Resistant Enterococcus Faecium," *Journal of Antimicrobial Chemotherapy* 26: 619-626 (1990).

Blenkham, J.I., et al., "Comparative In Vitro Activity of Daptomycin (LY146032) and Vancomycin against Gram-Positive Cocci Determined Using a Pharmacokinetic Model," Eur. J. Clin. Microbial. Infect. Dis. 8: 734-737 (1989).

Boaretti, Marzia, et al., "The Activity of Daptomycin on Enterococcus Faecium Protoplasts: Indirect Evidence Supporting a Novel Mode of Action on Lipoteichoic Acid Synthesis," *Journal of Antimicrobial Chemotherapy* 31: 227-235 (1993).

Boaretti, Marzia, et al., "Identification of Daptomycin-Binding Proteins in the Membrane of Enterococcus hirae," *Antimicrobial Agents and Chemotherapy* 39(9): 2068-2072 (Sept. 1995).

Bocci, Velio, "Catabolism of Therapeutic Proteins and Peptides with Implications for Drug Delivery," Advanced Drug Delivery Reviews 4: 149-169 (1990).

Bolton, Charles F., et al., "Critically III Polyneuropathy: Electrophysiological Studies and Differentiation from Guillain-Barré Syndrome," Journal of Neurology, Neurosurgery, and Psychiatry 49: 563-573 (1986).

Bush, Larry M., et al., "In Vitro Postantibiotic Effect of Daptomycin (LY146032) Against Enterococcus Faecalis and Methicillin-Susceptible and Methicillin-Resistant Staphylococcus Aureus Strains," Antimicrobial Agents and Chemotherapy 33: 1198-1200 (Aug. 1989).

Canepari, Pietro, et al., "Lipoteichoic Acid as a New Target for Activity of Antibiotics: Mode of Action of Daptomycin (LY146032)," Antimicrobial Agents and Chemotherapy 34: 1220-1226 (June 1990).

Carrier, Danielle, et al., "Modulation of Phospholipase  $A_2$  Activity by Aminoglycosides and Daptomycin: A Fourier Transform Infrared Spectroscopic Study," *Biochemistry* 37: 7589-7597 (1998).

Confer, A.W., et al., "Light and Electron Microscopic Changes in Cardiac and Skeletal Muscle of Sheep with Experimental Monensin Toxicosis," Veterinary Pathology 20: 590-602 (1983).

Couture, Michele, et al., "Daptomucin May Attenuate Experimental Tobramycin Nephrotoxicity by Electrostatic Complexation to Tobramycin," Antimicrobial Agents and Chemotherapy 38(4): 742-749 (Apr. 1994).

Craig, W.A., "Once-Daily Versus Multiple-Daily Dosing of Aminoglycosides," *Journal of Chemotherapy* 7(n.2): 47-52 (1995).

Debbia, Eugenio, et al., "In Vitro Activity of LY146032 Alone and in Combination with Other Antibodies against Gram-Positive Bacteria," *Antimicrobial Agents and Chemotherapy* 32(2): 279-281 (Feb. 1988).

De La Maza, Lorena, et al., "In Vitro Activities of Daptomycin and Other Antimicrobial Agents Against Vancomycin-Resistant Gram-Positive Bacteria," Antimicrobial Agents and Chemotherapy 33(8): 1383-1384 (August 1989).

Digranes, Asbjorn, et al., "In Vitro Activity of Daptomycin Against 297 Staphylococcal Isolates," Chmotherapy 36: 136-140 (1990).

Draper, Ruth P., "Studies on the Muscle Toxicant 2,3,5,6-Tetramethyl P-Phenylenediamine: Effects on Various Biomarkers including Urinary Creatine and Taurine," *Arch. Toxicol.* 69:111-117 (1994).

Drusano, George L., et al., "Pharmacodynamics of a Fluoroquinolone Antimicrobial Agent in a Neutropenic Rat Model of Pseudomonas Sepsis," Antimicrobial Agents and Chemotherapy 37(3): 483-490 (Mar. 1993).

Duh, Ruay-Wang, et al., "In Vitro Activity of 19 Antimicrobial Agents Against Enterococci from Healthy Subjects and Hospitalized Patients and Use of an ace Gene Probe from Enterococcus faecalis for Species Identification," *Microbial Drug Resistance* 7(1): 39-46 (2001).

Duška, F., et al., "The Pyrophosphate Heart Scintigram in Children with Progressive Muscular Dystrophy," Nucl. Med. 23: 189-191 (1984).

Ehlers, S., et al., "Influence of LY146032 (Daptomycin) on the Cell-Mediated Immunity," (Confidential Communication).

El-Mady, Abdelhady et al., "The Bactericidal Activity of Ampicillin, Daptomycin, and Vancomycin Against Ampicillin-Resistant Enterococcus Faecium," Diagn. Microbiol. Infect. Dis. 14: 141-145 (1991).

Eliopoulos, George M., et al., "In Vitro Activity and Mechanism of Action of A21978C<sub>1</sub>, a Novel Cyclic Lipopetide Antibiotic," *Antimicrobial Agents and Chemotherapy* 27(3): 357-362 (Mar. 1985).

Fass, Robert J., et al., "In Vitro Activity of LY146032 Against Staphylococci, Streptococci, and Enterococci," *Antimicrobial Agents and Chemotherapy* 30(5): 781-784 (Nov. 1986).

Fischer, W., "Physiology of Lipoteichoic Acids in Bacteria," Advances in Microbial Physiology 29: 234-303.

Fontana, Roberta, et al., "In Vitro Response to Bactericidal Activity of Cell Wall-Active Antibiotics Does Not Support the General Opinion that Enterococci are Naturally Tolerant to These Antibiotics," *Antimicrobial Agents and Chemotherapy* 34(8): 1518-1522 (Aug. 1990).

Freeman, Collin D., et al., "Once-Daily Dosing of Aminoglycosides: Review and Recommendation for Clinical Practice," *Journal of Antimicrobial Chemotherapy* 39: 677-686 (1997).

Fuchs, P.C., et al., "Daptomycin Susceptibility Tests: Provisional Criteria, Quality Control, and Importance of Ca++ Concentration in Test Media," Interscience Conference on Antimicrobial Agents and Chemotherapy Poster #350 (1999).

Golan, Y., et al., "Daptomycin for Line-Related Leuconostoc Bacteraemia," Journal of Antimicrobial Chemotherapy 47: 357-368 (2001).

Goldstein, E.J.C., et al., "In Vitro Activity of Daptomycin (Cidecin<sup>TM</sup>), Quinupristin/Dalfopristin, Linezolid and Vancomycin Against 275 Gram-Positive Aerobic and Anaerobic Organisms," *Interscience Conference on Antimicrobial Agents and Chemotherapy* Poster #2293 (2000).

Hanberger, Hakan, "Pharmacodynamic Effects of Antibiotics - Studies on Bacterial Morphology, Initial Killing, Postantibiotic Effect and Effective Regrowth Time," Linköping University Medical Dissertations No. 357 (1992).

Herscovici, Lisette, et al., "Efficacy and Safety of Once Daily Versus Intermittent Dosing of Tobramycin in Rabbits with Acute Pyelonephritis," Scand J Infect Dis. 20: 205-212 (1988).

Hiramatsu, K. "Reduced Susceptibility of Staphylococcus Aureus to Vancomycin," MMWR 46: 624-626 (July 11, 1997).

Hyatt, Judith M., et al., "The Importance of Phamacokinetic/Pharmacodynamic Surrogate Markers to Outcome: Focus on Antibacterial Agents," Clinical Pharmacokinetic Concepts 28(2): 143-160 (1995).

Jacobus, N.V., et al., "Effect of Daptomycin on Fecal Suspensions Seeded with a Vancomycin-Resistant Enterococcus," *Interscience Conference on Antimicrobial Agents and Chemotherapy* Poster #F-113 (1998).

Jacobus, N.V., et al., "In Vitro Activity of Daptomycin against Resistant Gram-Positive Pathogens," *Interscience Conference on Antimicrobial Agents and Chemotherapy* Abstract F-112 (1998).

Jones, Ronald N., et al., "Antimicrobial Activity and Spectrum of LY146032, a Lipopeptide Antibiotic, Including Susceptibility Testing Recommendations," *Antimicrobial Agents and Chemotherapy* 31(4): 625-629 (1987).

Jones, Ronald N., "Changing Patterns of Infection: A Global Picture," 8th International Congress on Infectious Diseases 200-209 (May 16, 1998).

King, Charles H., et al.. "Pharmacokinetics of Tobramycin and Gentamicin in Abusers of Intravenous Drugs," *Antimicrobial Agents and Chemotherapy* 27(3): 285-290 (Mar. 1985).

Kirsch, Lee E., et al., "Kinetics of the Aspartyl Tranpeptidation of Daptomycin, a Novel Lipopeptide Antibiotic," *Pharmaceutical Research* 6(5): 387-393 (1989).

Kreft, B., et al., "Experimental Studies on Nephrotoxicity and Pharmacokinetics of LY146032 (Daptomycin) in Rats," *Journal of Antimicrobial Chemotherapy* 25: 635-643 (1990).

Lakey, Jeremy H., et al., "Fluorescence Indicates a Calcium-Dependent Interaction between the Lipopeptide Antibiotic LY146032 and Phospholipid Membranes," *Biochemistry* 4641-4645 (1988).

Liebowitz, Lynne D., et al., "In Vitro Selection of Bacteria Resistant to LY146032, a New Cyclic Lipopeptide," Antimicrobial Agents and Chemotherapy 32:(1) 24-26 (Jan. 1988).

Louie, Arnold, et al., "Comparison of In Vitro Inhibitory and Bactericidal Activities of Daptomycin (LY 146032) and Four Reference Antibiotics, Singly and in Combination, against Gentamicin-Susceptible and High-Level-Gentamicin-Resistant Enterococci," Chemotherapy 39: 302-310 (1993).

Louie, Arnold, et al., "Pharmacodynamics of Daptomycin in a Murine Thigh Model of Staphylococcus aureus Infection," *Antimicrobial Agents and Chemotherapy* 45(3): 845-851 (Mar. 2001).

Lucas, Gregory, M., et al., "Vancomycin-Resistant and Vancomycin-Susceptible Enterococcal Bacteremia: Comparison of Clinical Features and Outcomes," *Clinical Infectious Diseases* 26: 1127-1133 (May 1998).

Lutz, H., et al., "Ototoxicity of Vancomycin: An Experimental Study in Guinea Pigs," ORL J. Otorhinolaryngol. Relat. Spec. 53: 273-278 (1991).

Malone, Donald A., et al., "Enterococcal Bacteremia in Two Large Community Teaching Hospitals," *The American Journal of Medicine* 81: 601-606 (October 1986).

Markowitz, Sheldon M., et al., "Antimicrobial Susceptibility and Molecular Epidemiology of B-Lactamase-Producing, Aminoglycoside-Resistant Isolates of Entercoccus Faecalis," *Antimicrobial Agents and Chemotherapy* 35(6): 1075-1080 (June 1991).

Mengin-Lecreulx, Dominique, et al., "Inhibition of Peptidoglycan Biosynthesis in Bacillus megaterium by Daptomycin," FEMS Microbiology Letters 69: 245-248 (1990).

Mobarakai, Neville, et al., "Bacterial Activities of Peptide Antibodies Against Multidrug-Resistant Enterococcus Faecium," Antimicrobial Agents and Chemotherapy 38(2): 385-387 (Feb. 1994).

Morris, Charles M., "Effect of Polymyxin B Nonapeptide on Daptomycin Permeability and Cell Surface Properties in Pseudomonas aeruginosa, Escherichia coli, and Pasteurella multocida," *The Journal of Antibiotics* 48(1): 67-72 (January 1995).

Mouton, R. Peter, et al., "LY146032: Activity and Resistance Development In Vitro," *Journal of Antimicrobial Chemotherapy* 20: 513-517 (1987).

Nicolau, David P., et al., "Experience with a Once-Daily Aminoglycoside Program Administered to 2,184 Adult Patients," *Antimicrobial Agents and Chemotherapy* 39(3): 650-655 (Mar. 1995).

Novilla, M.N., "The Veterinary Importance of the Toxic Syndrome Induced by Ionophores," *Vet. Hum. Toxicol.* 34(1):66-70 (Feb. 1992).

Oleson, Rick, et al., "Separate Mechanisms for the Schedule Dependence of Daptomycin's Toxicity and Efficacy," Sierra Biomedical Incorporated Annual Biotech Symposium Presentation (June 7 & 8, 1999).

Oleson, Rick, et al., "Once-Daily Dosing Decreases Toxicity of Daptomycin," 38th Annual Meeting Society of Toxicology Poster #1520 (March 14-18, 1999).

Oleson, Rick, et al., "Once-Daily Dosing Decreases Toxicity of Daptomycin," 9th European Congress of Clinical Microbiology and Infectious Diseases Poster #P0957A (March 21-24, 1999).

Oliver, N., et al., "In Vitro Studies on Resistance to the Lipopetide Antibiotic Daptomycin," Interscience Conference on Antimicrobial Agents and Chemotherapy Poster # F-117 (1998).

Periti, P., "Preclinical and Clinical Evaluation of Once-Daily Aminoglycoside Chemotherapy," *Journal of Chemotherapy* 7(4): 311-337 (1995).

Physician's Desk Reference, "Azactam for Injection," Bristol-Myers Squibb Co., 779-782.

Pittet, Didler, et al., "Microbiological Factors Influencing the Outcome of Nosocomial Bloodstream Infections: A 6-Year Validated, Population-Based Model," Clinical Infectious Diseases 24: 1068-1078 (June 24, 1997).

Pohlod, Donald J., "In-Vitro Susceptibility of Gram-Positive Cocci to LY146032 Teicoplanin, Sodium Fusidate, Vancomycin, and Rifampicin," *Journal of Antimicrobial Chemotherapy* 20: 197-202 (1987).

Powell, S.H., "Once-Daily vs. Continuous Aminoglycoside Dosing; Efficacy and Toxicity in Animal and Clinical Studies of Gentamicin, Netilmicin, and Tobramycin," *The Journal of Infectious Diseases* 147(5): 918-932 (May 1983).

Preston, Sandra L., "Pharmacodynamics of Levofloxacin: A New Paradigm for Early Clinical Trials," *JAMA* 279(2): 125-129 (January 14, 1998).

Rice, Louis B., et al., "In Vitro Synergism between Daptomycin and Fosfomycin against Enterococcus faecalis Isolates with High-Level Gentamicin Resistance," Antimicrobial Agents and Chemotherapy 33(4): 470-473 (Apr. 1989).

Rowland, Malcolm, et al., "Interacting Drugs," in <u>Clinical</u> Pharmacokinetics - Concepts and Applications, Ch. 17, 272-273 (1995).

Rybak, Michael J., et al., "Bactericidal Killing Rate and Pharmacokinetics of Daptomycin and Vancomycin in Intravenous Drug Abusers Being Treated for Staphylococcus Aureus Endocarditis," *Pharmacotherapy* 11(1): 98 (1991).

Rybak, Michael J., et al., "Vancomycin Pharmacokinetics in Burn Patients and Intravenous Drug Abusers," *Antimicrobial Agents and Chemotherapy* 34(5): 792-795 (May 1990).

Rybak, Michael J., et al., "Teicoplanin Pharmacokinetics in Intravenous Drug Abusers Being Treated for Bacterial Endocarditis," *Antimicrobial Agents and Chemotherapy* 35(4): 696-700 (Apr. 1991).

Rybak, Michael J., et al., "Comparative In Vitro Activity of Daptomycin versus Vancomycin, Linezolid, and Synercid against Methicillin-Resistant and Susceptible Staphylococci, Vancomycin-Intermediate Susceptible Staphylococcus Aureus (VISA) and Vancomycin-Susce," Interscience Conference on Antimicrobial Agents and Chemotherapy Abstract C-146 (1998).

Rybak, Michael J., et al., "In Virto Activities of Daptomycin, Vancomycin, Linezolid, and Quinupristin-Dalfopristin Against Staphylococci and Enteroococi, Including Vancomycin-Intermediate and Resistant Strains," Antimicrobial Agents and Chemotherapy 44(4): 1062-1066 (Apr. 2000).

Salles, Monica S., "Ionophore Antibiotic (Narasin) Poisoning in Rabbits," Vet. Human Toxicol. 36(5): 437-444 (October 1994).

Schoenberg, M.H., et al., "Outcome of Patients with Sepsis and Septic Shock After ICU Treatment," *Langenbeck's Arch. Surg.* 383: 44-48.

Silva, M., et al., "In Vitro Activity of LY146032 Against Gram-Positive Bacteria," *Diagn. Microbiol. Infect. Disease* 9: 79-85 (1988).

Silverman, Jared A., et al., "Resistance Studies with Daptomycin," Antimicrobial Agents and Chemotherapy 45(6): 1799-1802 (June 2001).

Smith, K., et al., "Daptomycin Versus Vancomycin Treatment for Staphylococcus aureus Bacteremia in a Murine Model," *Chemotherapy* 36: 428-434 (1990).

Snydman, D.R., et al., "Comparative In Vitro Activities of Daptomycin and Vancomycin Against Resistant Gram-Positive Pathogens," *Antimicrobial Agents and Chemotherapy* 44(12): 3447-3450 (Dec. 2000).

Tally, F.P., et al., "Daptomycin (Cidecin™) Treatment for Serious Gram-Positive Infections Including Endocarditis," European Congress of Clinical Microbiology and Infectious Diseases WeP233:8/1 (2000).

Tally, F.P., et al., "Development of Daptomycin for Gram-Positive Infections," *Journal of Antimicrobial of Chemotherapy* 46: 523-526 (2000).

Tawfik, A.F., "Effects of Vancomycin, Teicoplanin, Daptomycin and Coumermycin on Normal Immune Capabilities," *Journal of Chemotherapy* 3(4): 226-231 (1991).

Thibault, Nathalie, et al., "Attenuation by Daptomycin of Gentamicin-Induced Experimental Nephrotoxicity," *Antimicrobial Agents and Chemotherapy* 38(5): 1027-1035 (May 1994).

Tripodi, Marie-Francoise, et al., "Influence of Subinhibitory Concentrations of Loracarbef (LY 163892) and Daptomycin (LY 146032) on Bacterial Phagocytosis, Killing and Serum Sensitivity," *Journal of Antimicrobial Chemotherapy* 26: 491-501 (1990).

Tymms, K.E., et al., "Correlation Between Tests of Muscle Involvement and Clinical Muscle Weakness in Polymyositis and Dermatomyositis," *Clinical Rheumatology* 9(4): 523-529 (1990).

Valentine, Beth A., "Increased Serum Alanine Aminotransferase Activity Associated with Muscle Necrosis in the Dog," *Journal of Veterinary Internal Medicine*, 4(3): 140-143.

Van Der Auwera, P., et al., "Influence of Antibiotics on Motility and Adherence of Human Neutrophils Studied In Vitro," *Drugs Exptl. Clin. Res.* 15(5): 211-218 (1989).

Vance-Bryan, Kyle, et al., "Investigation of the Early Killing of Stapylococcus Aureus by Daptomycin by Using an In Vitro Pharmacodynamic Model," Antimicrobial Agents and Chemotherapy 36(10): 2334-2337 (Oct. 1992).

Verbist, L., "In Vitro Activity of LY146032, a New Lipopeptide Antibiotic, against Gram-Positive Cocci," *Antimicrobial Agents and Chemotherapy* 31(2): 340-342 (Feb. 1987).

Vogelman, Bennett, et al., "Kinetics of Antimicrobial Activity," Journal of Pediatrics 108(2):835-840 (May 1986).

٠. .

- Weinstein, Melvin P., et al., "The Clinical Significance of Positive Blood Cultures in the 1990s: A Prospective Comprehensive Evaluation of the Microbiology, Epidemiology, and Outcome of Bacteremia and Fungemia in Adults," Clinical Infectious Diseases 24: 584-602 (April 1997).
- Zamora, S., et al., "Elevated Aminotransferase Activity as an Indication of Muscular Dystrophy: Case reports and review of the Literature," *Clinical Gastroenterology* 10(6): 389-393 (Oct. 1996).
- Brown, S.D., et al., "In Vitro Activity of Daptomycin (Cidecin™) Against Contemporary Gram-positive Clinical Bacterial Isolates From 11 North American Medical Centers (NAMC), European Congress of Clinical Microbiology and Infectious Diseases Poster #P90:5/5 (2000).
- DeBruin, Michael F., "Efficacy and Safety of Daptomycin for the Treatment of Bacteremia and Serious Infections Due to Gram-positive Bacteria," 4<sup>th</sup> Decennial International Conference on Nosocomial and Healthcare-Associated Infections Poster #594 P-S2-37 (March 5-9, 2000).
- Fuchs, Peter C., et al., "Daptomycin Susceptibility Tests: Interpretive Criteria, Quality Control, and Effect of Calcium on In Vitro Tests, *Diagnostic Microbiology and Infectious Disease* 38: 51-58 (2000).
- Heine, H.S., et al., "In Vitro Activity of Daptomycin, Sparfloxacin, Quinupristin-Dalfopristin and Other Antibiotics Against Bacillus anthracis Strains," Interscience Conference on Antimicrobial Agents and Chemotherapy Poster #517 (2000).
- Kaatz, G.W., et al., "Development of Daptomycin Resistance (D') in Experimental Staphylococcus aureus (SA) Endocarditis," 33<sup>rd</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy Abstract #155 (1993).
- Safdar, N., et al., "In-Vivo Pharmacodynamics of Daptomycin (DAP)," Infectious Disease Society of America Abstract (November 1999).
- Tozzi, S., et al., "Successful Treatment of Leuconostoc Species Bacteremia in Recipients of Bone Marrow Transplantation (BMT) by Daptomycin (D)," Clinical Microbiology and Infection Abstract and Poster, Abstract # WeP309. Clinical Microbiology and Infection Vol. 6, Supp. 1, Page 240 (May 2000).

Applicants request that the cited documents be (1) fully considered by the Examiner during the course of examination of this application and (2) printed on

any patent issuing from this application.

Respectfully submitted,

James F. Haley, Jr. (Reg. No. 27,794)

Attorney for Applicants Karen E. Brown (Reg. No. 43,866)

Karen E. Brown (Reg. No. 43,866) Agent for Applicants

c/o FISH & NEAVE

1251 Avenue of the Americas New York, NY 10020-1104

Tel: (212) 596-9000